REMARKS

The Official Action dated September 25, 2003 has been carefully considered. Accordingly, the changes presented herewith, taken with the following remarks, are believed sufficient to place the present application in condition for allowance. Reconsideration is respectfully requested.

By the present Amendment, claims 1, 14, 15, 20 and 23 are amended for matters of form and clarity. Claim 20 is also amended to recite that all of the detection zones are downstream of all of the calibrator zones in accordance with the teachings of the specification. Claims 33-39 are added. Claim 33 also recites that all of the detection zones are downstream of all of the calibrator zones in the lateral flow matrix, as set forth throughout the present specification. Claims 34-39 further define Reactant* in accordance with the teachings of the specification at page 17, line 20 - page 18, line 10. It is believed that these changes do not involve any introduction of new matter, whereby entry is believed to be in order and is respectfully requested.

In the Official Action, claim 1, part (iii) was objected to as the Examiner asserted that the term "obtaining" should be "determining". As the preamble of claim 1 recites a lateral flow method for the determination of an analyte in a sample, step (iii) of claim 1 has been amended to recite determining the amount of analyte in the sample as suggested by the Examiner. It is therefore believed that the rejection has been overcome. Reconsideration is respectfully requested.

Claims 1-4, 6 and 11-32 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner asserted that several portions of claims 1, 14, 20 and 23 were vague and indefinite.

This rejection is traversed. More particularly, the Examiner's comments have been carefully reviewed and while it is believed that the previous claims were sufficiently clear and

definite to comply with the requirements of 35 U.S.C. §112, second paragraph, claims 1, 12, 14, 20 and 23 have been revised to clarify the language asserted by the Examiner as being vague and indefinite. It is believed that the present claims are definite to one of ordinary skill in the art and particularly point out and distinctly claim the subject matter which Applicants regard as the invention in accordance with the requirements of 35 U.S.C. §112, second paragraph. It is therefore believed that the rejection has been overcome and reconsideration is respectfully requested.

Claims 1-3, 6, 11-18, 20-25 and 27-32 have been rejected as being obvious and unpatentable over the Rylatt et al PCT application WO 97/09620 in view of the Van Deusen et al U.S. Patent No. 5,132,097. The Examiner asserted that Rylatt et al disclose a lateral flow permeable medium comprising a calibration zone and a test/detection zone wherein the test/detection zone is downstream of the calibration zone, and the Examiner referred to Figures 2, 5 and 8. The Examiner acknowledged that Rylatt et al fail to teach that the calibrator and the analyte biospecifically bind to Reactant* by equivalent binding sites. However, the Examiner relied on Van Deusen et al as disclosing a test strip with a standard area/calibration zone and a test area/detection zone wherein a labeled reagent binds to both calibrator and analyte. In response to Applicants' previous arguments, the Examiner asserted that the present claims recite one or more calibration zones and one or more detection zones downstream of the one or more calibration zones.

However, Applicants submit that the methods and devices defined by claims 1-3, 6, 11-18, 20-25 and 27-32 are nonobvious over and patentably distinguishable from Rylatt et al in view of Van Deusen et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

More particularly, as defined by claim 1, the invention is directed to a lateral flow method for the determination of an analyte in a sample using biospecific affinity reactions.

The method comprises forming a complex in a lateral flow matrix, the complex comprising Reactant I---Analyte'---Reactant*, where Reactant* and Reactant I exhibit biospecific affinity to the analyte, Reactant* is analytically detectable, and Analyte' is the analyte or an analyte-related reactant. The method further comprises subsequently determining a detectable signal constituting a sample value from Reactant* in the complex, and determining the amount of analyte in the sample by comparing the sample value with one or more calibrator values, each of which corresponds to a standard amount of analyte. Before determination of the calibrator value, either (i) calibrator, or (ii) a binder for the calibrator has been bound to a matrix, and when a binder for the calibrator has been bound to the matrix, calibrator is added or calibrator predeposited in the matrix is released for binding with the binder, and the matrix is insoluble in the liquid medium in which binding of Reactant* to the calibrator occurs. The calibrator and the analyte exhibit biospecific affinity to Reactant* by equivalent binding sites. One or more calibrator zones CZ comprising calibrator or binder for the calibrator are located in a single process flow stream with Reactant I in a detection zone DZ.

As defined by claim 20, the invention is directed to a device for transforming measured signal values of a complexed, analytically detectable reactant (Reactant*) to real amounts of analyte in a sample, in connection with performing an analysis method using biospecific affinity reactions for the determination of the amount of analyte in a sample, to form complexes comprising Reactant* in an amount which is related to the amount of analyte in the sample. The device comprises a flow matrix in which there is an area of process flow for the transport of Reactant*. In the process flow area are (i) one or more calibrator zones (CZ) comprising a calibrator, or binder for the calibrator, which is firmly anchored to the matrix, the amounts of calibrator or calibrator binder, respectively, being different for at least two calibrator zones when at least two calibrator zones are present, and the calibrator exhibiting binding sites to which Reactant* binds, when Reactant* is transported through a

calibrator zone, (ii) an application zone for Reactant* ($A_{R^*}Z$) upstream of the calibrator zones, and (iii) one or more detection zones (DZ). All of the detection zones are downstream of all of the calibrator zones.

The methods and devices according to the present invention provide improvements in analyte determinations employing calibrators. Particularly, the present methods enable compensation for the differences that may exist between calibrator and sample solution and between runs performed at different times and/or different places. These advantages are obtained by the defined methods of claim 1, employing Reactant* which binds to either analyte or calibrator, and forming the complex in the flow matrix and wherein the calibrator zone or zones are located in the same process flow as the detection zone for measuring analyte. Similarly, these advantages are obtained by the defined devices of claim 20, employing one or more calibrator zones and one or more detection zones, with all of the detection zones being downstream of all of the calibrator zones, the calibrator exhibiting binding sites to which Reactant* binds when Reactant* is transported through a calibrator zone, and an application zone for Reactant* upstream of the calibrator zones.

Rylatt et al disclose a method and device for determination of an analyte in a sample. With reference to Fig. 2 cited by the Examiner, the Rylatt et al device includes a test zone 204 arranged between calibration zones 210 and 211. Thus, all of the detection or test zones are not downstream of all of the calibration zones as required by claim 20, but interspersed therein. Moreover, Applicants find no teaching or suggestion by Rylatt et al of a method or device employing Reactant* as presently claimed, binding to both calibrator and analyte as recited in claim 1. Rather, as shown in Fig. 2 of Rylatt et al, the procedure of Rylatt et al employs an analyte detection agent 208 for binding in the test zone and a separate calibration agent 209 for binding in the calibration zone. Further, the procedure described in Fig. 2 of Rylatt et al employs a separate support element for diffusibly attaching the analyte detection

agent 208 and the calibration agent 209, and Applicants find no teaching or suggestion by Rylatt et al as to where such elements would be provided in the flow matrix 207.

The Examiner has relied on Van Deusen et al to resolve the deficiencies of Rylatt et al. While Van Deusen et al disclose a test strip including a standard or control area 16 containing a known amount of Reactant B (analyte) bound to Reactant A, Van Deusen et al provide no teaching or suggestion relating to a lateral flow method or for replacing the distinct labeled calibration agent/calibration agent receptor binding pair of Rylatt et al with a calibrator as presently claimed, which together with analyte exhibits biospecific affinity to Reactant* by equivalent binding sites. Only in hindsight of the presently claimed methods would one of ordinary skill in the art be motivated to combine the teachings of Van Deusen et al, which are more specifically directed to the use of a laser for detecting a light pattern through the reactive surface, with the lateral flow method and apparatus of Rylatt et al in order to obtain the advantage of avoiding process variations between testing and calibration which are avoided according to the present methods and devices.

Moreover, if the teachings of Van Deusen et al are combined with Rylatt et al as asserted by the Examiner, such a combination does not result in either the method of claim 1 or the device of claim 20. That is, neither Rylatt et al nor Van Deusen et al teach a lateral flow matrix method wherein a single analytically detectable reactant may be empkoyed, as in claim 1. Moreover, neither Rylatt et al nor Van Deusen et al teach a flow matrix wherein all detection zones are downstream of all calibration zones.

Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention absent some teaching, suggestion or incentive supporting the combination, *In re Geiger*, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987). Rylatt et al and Van Deusen et al provide no teaching, suggestion or incentive for combining their teachings along the lines of the presently claimed method and device, and particularly provide no teaching or

suggestion of the advantages taught in the present specification. Thus, Rylatt et al and Van Deusen et al do not render the presently claimed method and device obvious. It is therefore submitted that the methods and devices defined by claims 1-3, 6, 11-18, 20-25 and 27-32 are nonobvious over and patentably distinguishable from the combination of Rylatt et al and Van Deusen et al, whereby the rejection under 35 U.S.C. §103 has been overcome. Reconsideration is respectfully requested.

Claim 19 has been rejected as being obvious and unpatentable over Rylatt et al and Van Deusen et al in view of the Self et al U.S. Patent No. 4,446,231. The Examiner relied on Self et al as teaching diagnosis of an autoimmune disease.

However, Applicants submit that the methods defined by claim 19 are nonobvious over and patentably distinguishable from the teachings of Rylatt et al, Van Deusen et al and Self. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

The deficiencies of Rylatt et al and Van Deusen et al with respect to claim 1, on which claim 19 depends, are discussed in detail above. Self does not resolve these deficiencies. That is, Self discloses an immunoassay employing an enzyme label which converts a precursor into a cycling factor which in turn is interconverted in a cycling detection system. Applicants find no teaching or suggestion by Self relating to a lateral flow method wherein a complex is formed in a lateral flow matrix using Reactant* to which both analyte and calibrator bind as defined in present claim 1 and employing one or more calibration zones, particularly in the same process flow as a detection zone.

In order to render a claimed invention obvious, the prior art must enable one skilled in the art to make and use the claimed invention, *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 U.S.P.Q.2d 1481, 1489 (Fed. Cir. 1997). In view of the failure of Rylatt et al, Van Deusen et al and Self to teach a lateral flow method as claimed, the combination of these references does not enable one of ordinary skill in the art to conduct the method of claim 1 and therefore

does not render claim 1, or claim 19 dependent thereon, obvious. It is therefore submitted that the rejection of claim 19 under 35 U.S.C. §103 based on Rylatt et al, Van Deusen et al and Self has been overcome. Reconsideration is respectfully requested.

Claims 4 and 26 have been rejected as being obvious and unpatentable over Rylatt et al and Van Deusen et al in view of the Weng et al U.S. Patent No. 4,740,468. The Examiner relied on Weng et al as disclosing the use of a specific binding partner that is biospecific to a second binding partner which in turn is specific for an analyte. The Examiner asserted it would have been obvious to incorporate an immobilized specific binding partner as taught by Weng et al in the device of Rylatt et al.

However, Applicants submit that the method and device defined by claims 4 and 26 are nonobvious over and patentably distinguishable from the combination of Rylatt et al, Van Deusen and Weng et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

The deficiencies of Rylatt et al and Van Deusen et al have been discussed above with respect to claim 1 and claim 20, on which claim 4 and claim 26 depend, respectively, and are not resolved by Weng et al. That is, Weng et al disclose a method and device for determining the presence of an analyte in a sample suspected of containing the analyte. Applicants find no teaching or suggestion by Weng et al for modifying the device of Rylatt et al in accordance with the method and device as recited in claims 1 and 20, wherein all of the the detection or test zones are downstream of the all of the calibration zones, a single Reactant* as presently claimed, binding to both calibrator and analyte, is employed in a lateral flow matrix, and/or where such Reactant* is arranged in the flow matrix. Thus, Weng et al do not resolve the deficiencies of Rylatt et al and Van Deusen et al. It is therefore submitted that the rejection under 35 U.S.C. §103 based on these references has been overcome. Reconsideration is respectfully requested.

It is believed that the above represents a complete response to the rejections under 35 U.S.C. §§103 and 112, second paragraph, and places the present application in condition for allowance. Reconsideration and an early allowance are requested.

Respectfully submitted,

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